Answer 1:

Bibliographic Information

Gene expression predicts differential capecitabine metabolism, impacting on both pharmacokinetics and antitumor activity. Guichard, Sylvie M.; Macpherson, Janet S.; Mayer, Iain; Reid, Eilidh; Muir, Morwenna; Dodds, Michael; Alexander, Susan; Jodrell, Duncan I. Cancer Research UK Pharmacology and Drug Development Group, Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh, UK. European Journal of Cancer (2008), 44(2), 310-317. Publisher: Elsevier Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 149:167255 AN 2008:82554 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Capecitabine is converted into 5'-deoxy-5-fluorocytidine (5'DFCR), 5'-deoxy-5-fluorouridine (5'DFUR) and 5-fluorouracil (5-FU) by CES1 and 2, CDD, and TP, in both liver and tumor. 5-FU is catabolized by DPD. Gene expression anal. of these enzymes was undertaken in fresh human hepatocytes, mouse liver, colorectal cancer cell lines and xenografts. Cell lines with low CDD expression (<1.5) had 5'DFCR/5'DFUR cytotoxicity ratios >2 and cell lines with TP/DPD < 0.6 had 5'DFUR IC50 > 50 μM (SRB assay). A pharmacokinetic/pharmacodynamic study in nude mice bearing HCT 116 xenografts and treated with capecitabine by oral gavage assessed pharmacokinetic, gene expression and antitumor activity. Low liver CDD correlated with high 5'DFCR plasma concns. in mice. CDD expression was .apprx.100-fold higher in fresh human hepatocytes than mouse liver, explaining the higher plasma 5'DFUR concns. reported previously in humans. Tumor 5-FU concn. correlated with TP/DPD and with tumor response. These studies identify the potential utility of gene expression anal. and drug monitoring in tumor in patients.

Answer 2:

Bibliographic Information

Changes to the dihydropyrimidine dehydrogenase gene copy number influence the susceptibility of cancers to 5-FU-based drugs: Data mining of the NCI-DTP data sets and validation with human tumour xenografts. Kobunai, Takashi; Ooyama, Akio; Sasaki, Shin; Wierzba, Konstanty; Takechi, Teiji; Fukushima, Masakazu; Watanabe, Toshiaki; Nagawa, Hirokazu. Department of Systematic Clinical Oncology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan. European Journal of Cancer (2007), 43(4), 791-798. Publisher: Elsevier Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 147:1058 AN 2007:213726 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Patient response to the anti-tumor drug 5-fluorouracil (5-FU) is variable, but predicting the response rate is important for the selection of effective chemotherapy. Our aim was to identify alterations in DNA copy no. that influence susceptibility of cancer cells to 5-FU-based drugs. The NCI public database was used to identify chromosome loci assocd. with drug sensitivity and DNA copy no. One of the 11 candidates, the cytogenetic band 1p21.3, harbors the dihydropyrimidine dehydrogenase (DPD) gene. To validate this finding, the DPD copy no. and in vivo sensitivity to 5-FU-based drugs were detd. in 31 human tumor xenografts. Those xenografts demonstrating low sensitivity had significantly higher DPD copy nos. than highly sensitive tumors (P < 0.002). Moreover, DPD mRNA expression levels were significantly correlated with DPD copy nos. (P < 0.046). An assessment of copy no. may be a more precise method of predicting the sensitivity of cancer patients to 5-FU related drugs.

Answer 3:

Bibliographic Information

Gene expression analysis using human cancer xenografts to identify novel predictive marker genes for the efficacy of 5-fluorouracil-based drugs. Ooyama, Akio; Takechi, Teiji; Toda, Etsuko; Nagase, Hideki; Okayama, Yoshihiro; Kitazato, Kenji; Sugimoto, Yoshikazu; Oka, Toshinori; Fukushima, Masakazu. Optimal Medication Research Laboratory, Taiho Pharmaceutical

Company, 224-2 Ebisuno, Hiraishi, Kawauchi-cho Tokushima, Japan. Cancer Science (2006), 97(6), 510-522. Publisher: Blackwell Publishing Asia Pty Ltd., CODEN: CSACCM ISSN: 1347-9032. Journal written in English. CAN 145:410188 AN 2006:609074 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The development of a diagnostic method for predicting the therapeutic efficacy or toxicity of anticancer drugs is a crit. issue. We carried out a gene expression anal. to identify genes whose expression profiles were correlated with the sensitivity of 30 human tumor xenografts to 5-fluorouracil (5-FU)-based drugs (tegafur + uracil [UFT], tegafur + gimeracil + oteracil [S-1], 5'-deoxy-5-fluorouridine [5'-DFUR], and N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine [capecitabine]), as well as three other drugs (cisplatin [CDDP], irinotecan hydrochloride [CPT-11], and paclitaxel) that have different modes of action. In the present study, we focused esp. on the fluoropyrimidines. The efficacy of all anticancer drugs was assayed using human tumor xenografts in nude mice. The mRNA expression profile of each of these xenografts was analyzed using a Human Focus array. Correlation anal. between the gene expression profiles and the chemosensitivities of seven drugs identified 39 genes whose expression levels were correlated significantly with multidrug sensitivity, and we suggest that the angiogenic pathway plays a pivotal role in resistance to fluoropyrimidines. Furthermore, many genes showing specific correlations with each drug were also identified. Among the candidate genes assocd. with 5-FU resistance, the dihydropyrimidine dehydrogenase mRNA expression profiles of the tumors showed a significant neg. correlation with chemosensitivity to all of the 5-FU based drugs except for S-1. Therefore, the administration of S-1 might be an effective strategy for the treatment of high dihydropyrimidine dehydrogenase-expressing tumors. The results of the present study may enhance the prediction of tumor response to anticancer drugs and contribute to the development of tailor-made chemotherapy.

Answer 4:

Bibliographic Information

Simultaneous determination of capecitabine and its metabolites by HPLC and mass spectrometry for preclinical and clinical studies. Guichard, Sylvie M.; Mayer, Iain; Jodrell, Duncan I. Pharmacology and Drug Development Team, Cancer Research UK Centre, University of Edinburgh, Edinburgh, UK. Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2005), 826(1-2), 232-237. Publisher: Elsevier B.V., CODEN: JCBAAI ISSN: 1570-0232. Journal written in English. CAN 143:378962 AN 2005:1105446 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A reverse-phase high-performance liq. chromatog. method with electrospray ionization and detection by mass spectrometry is described for the simultaneous detn. of capecitabine, its intermediate metabolites (DFCR, DFUR) and the active metabolite 5-fluorouracil in mouse plasma, liver and human xenograft tumors. The method was also cross-validated in human plasma and human tumor for clin. application. The method has greater sensitivity than previously published methods with an equiv. accuracy and precision. It uses less biol. material (plasma, tissue) and should therefore be applicable to biopsies in patients treated with capecitabine.

Answer 5:

Bibliographic Information

Enhancement of antitumor activity of 5'-deoxy-5-fluorouridine (Furtulon) by taxane in human gastric cancer xenografts. Sawada, Noriaki; Nose, Taeko; Ishikawa, Tohru; Yutaka, Tanaka. Product Research Department, Chugai Pharmaceutical Co., Ltd., Kamakura, Kanagawa, Japan. Oncology Reports (2005), 14(1), 53-57. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 143:146059 AN 2005:624270 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

5'-Deoxy-5-fluorouridine (5'-DFUR, Furtulon) is activated to 5-fluorouracil (5-FU) by thymidine phosphorylase (dThdPase) highly expressed in many types of tumors. In previous studies, we demonstrated that taxanes (paclitaxel or docetaxel) up-regulated the tumor levels of dThdPase and enhanced the efficacy of 5'-DFUR in human colon and mammary xenograft models. In the present study, combination therapy of 5'-DFUR with taxanes in human gastric cancer xenograft models also showed, at the least, additive antitumor activity without significant augmentation of toxicity. Furthermore, paclitaxel up-regulated dThdPase expression in the tumor tissues as confirmed with ELISA and immunohistochem. These results suggest taxanes would potentiate the efficacy of 5'-DFUR by up-regulating-the tumor levels of dThdPase in gastric xenograft models. Clin. trials of 5'-DFUR in combination with taxane against gastric cancer are warranted.

Answer 6:

Bibliographic Information

Correlations between antitumor activities of fluoropyrimidines and DPD activity in lung tumor xenografts. Takechi, Teiji; Okabe, Hiroyuki; Ikeda, Kazumasa; Fujioka, Akio; Nakagawa, Fumio; Ohshimo, Hideyuki; Kitazato, Kenji; Fukushima, Masakazu. Cancer Research Laboratory, Taiho Pharmaceutical Co., Ltd., Hanno-city, Saitama, Japan. Oncology Reports (2005), 14(1), 33-39. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 143:146057 AN 2005:624267 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The purposes of this study were to evaluate the antitumor activity of S-1 (1 M tegafur, 0.4 M 5-chloro-2,4-dihydroxypyridine and 1 M potassium oxonate) on human lung tumor xenografts, as compared with other fluoropyrimidines, and to investigate the relationships between fluoropyrimidine antitumor activities and four distinct enzymic activities involved in the phosphorylation and degrdn. pathways of 5-fluorouracil (5-FU) metab. S-1, UFT (1 M tegafur - 4 M uracil), 5'-deoxy-5-fluorouridine (5'-DFUR), capecitabine and 5-FU were administered for 14 consecutive days to nude mice bearing lung tumor xenografts. S-1 showed stronger tumor growth inhibition in four of the seven tumors than the other drugs. Cluster anal., on the basis of antitumor activity, indicated that S-1/UFT and 5'-DFUR/capecitabine/5-FU could be classified into another group. We investigated tumor thymidylate synthase content, dihydropyrimidine dehydrogenase (DPD) activity, thymidine phosphorylase (TP) activity and orotate phosphoribosyl transferase activity in seven human lung tumor xenografts and performed regression analyses for the antitumor activities of fluoropyrimidines. There were inverse correlations between antitumor and DPD activities for 5'-DFUR (r=-0.79, P=0.034), capecitabine (r=-0.56, P=0.19) and 5-FU (r=-0.86, P=0.013). However, no such correlations were obsd. for S-1 and UFT. These findings suggest that S-1 contg. a potent DPD inhibitor may have an antitumor effect on lung tumors, with high basal DPD activity, superior to those of other fluoropyrimidines.

Answer 7:

Bibliographic Information

Sequential Treatment with Irinotecan and Doxifluridine: Optimal Dosing Schedule in Murine Models and in a Phase I Study for Metastatic Colorectal Cancer. Mishima, Hideyuki; Kato, Takeshi; Yanagisawa, Mieko; Tsujinaka, Toshimasa; Nishisho, Isamu; Tsujie, Masaki; Fujimoto-Ouchi, Kaori; Tanaka, Yutaka; Kikkawa, Nobuteru. Department of Surgery, Osaka National Hospital, Osaka, Japan. Chemotherapy (Basel, Switzerland) (2005), 51(1), 32-39. Publisher: S. Karger AG, CODEN: CHTHBK ISSN: 0009-3157. Journal written in English. CAN 142:441410 AN 2005:296045 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Irinotecan (CPT-11) and doxifluridine (5'-DFUR) are active agents against colorectal cancer. Each drug, however, has the possibility of causing diarrhea. First, the authors detd. the optimal dosing regimen in murine models. CPT-11 (i.v., q2d $\times$3) and 5'-DFUR (p.o., qd $\times$14) were administered to mice bearing a human colorectal cancer xenograft model. Diarrhea was stronger in the simultaneously administered schedule but not much stronger in the sequentially administered schedule compared with monotherapies. Both schedules yielded similar antitumor efficacies. Next, the authors conducted a phase I study combining CPT-11 on days 1 and 15, and 5'-DFUR

on days 3-14 and 17-28 every 5 wk in 19 patients with metastatic colorectal cancer. The doses of CPT-11 ranged from 80 to 150 mg/m2 and those of 5'-DFUR from 800 to 1,200 mg. Diarrhea of grade 3/4 developed in only 1 patient at 100 mg/m2/800-mg doses. Dose-limiting toxicities were hyperbilirubinemia and skipping doses due to fatigue at 150 mg/m2/1,200-mg doses. For the phase II study, the recommended dose was set at CPT-11 150 mg/m2 and 5'-DFUR 800 mg.

Answer 8:

Bibliographic Information

Dependence of chemotherapy response on p53 mutation status in a panel of human cancer lines maintained in nude mice. Koike, Masako; Fujita, Fumiko; Komori, Kinuyo; Katoh, Fumitaka; Sugimoto, Takuji; Sakamoto, Yasuo; Matsuda, Masato; Fujita, Masahide. Experimental Cancer Chemotherapy Research Laboratory Co., Ltd., Osaka, Japan. Cancer Science (2004), 95(6), 541-546. Publisher: Japanese Cancer Association, CODEN: CSACCM ISSN: 1347-9032. Journal written in English. CAN 141:343028 AN 2004:613610 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In contrast to findings in vitro, the clin. response to anticancer chemotherapy is not simply assocd. with the p53 mutation status. To analyze the relation between the actual response of solid tumors with p53 mutation and other biol. characteristics, we used a human cancer-nude mouse panel of 21 lines derived from stomach, colorectal, breast, lung, and liver cancers for exptl. chemotherapy. We examd. the tumor growth rates of the cancer lines and the effects of nine drugs in clin. use, namely, mitomycin C (MMC), cisplatin (CDDP), nimustine hydrochloride (ACNU), irinotecan (CPT-11), cyclophosphamide (CPA), 1-(2-tetrahydrofuryl)-5-fluorouracil (FT-207), a 4:1 mixt. of uracil and FT-207 (UFT), 5'-deoxy-5-fluorouridine (5'-DFUR), and adriamycin (ADM), on these tumors. The chemotherapy response was expressed as the tumor growth inhibition rate (IR). The genomic DNA sequences of the p53 gene in exons 5 through 8 were analyzed in these cancer tissues, and p53 mutations were detected in 10 of the 21 cancer lines (48%). Resistance to MMC was obsd. in p53 mutant tumors with smaller IRs than those for wild-type tumors (57.7% vs. 79.9%, P<0.03). No significant differences were noted with the other eight drugs. To explore the role of the p53 function in the chemotherapy response, we calcd. the correlation coeffs. between chemosensitivity and tumor growth rate sep. in p53 mutant and wild-type groups. In the p53 wild-type group, we found a pos. correlation for the following drugs: ADM (P<0.02), ACNU (P<0.007), CPA (P<0.011), UFT (P<0.012), and FT-207 (P<0.02). In the p53 mutant group, only CPA (P<0.003) showed a pos. correlation. The kinetics suggests that in the wild-type tumors, DNA damage caused by anticancer drugs occurs proportionally to the rate of DNA synthesis, and p53-mediated apoptosis is subsequently induced. The low frequency of pos. correlation in the p53 mutant tumors is compatible with the loss of function or malfunction of mutant p53.

The present results provide kinetic evidence that p53 function affects the response to anticancer drugs. Preserved p53 function tended to confer good chemosensitivity on rapidly growing tumors. However, the p53 mutation status did not seem to be suitable for use as an exclusive indicator to predict the chemotherapy response of human cancer xenografts.

Answer 9:

Bibliographic Information

Noninvasive measurements of capecitabine metabolism in bladder tumors overexpressing thymidine phosphorylase by fluorine-19 magnetic resonance spectroscopy. Chung, Yuen-Li; Troy, Helen; Judson, Ian R.; Leek, Russell; Leach, Martin O.; Stubbs, Marion; Harris, Adrian L.; Griffiths, John R. Department of Basic Medical Sciences, Cancer Research United Kingdom Biomedical Magnetic Resonance Group, St. George's Hospital Medical School, London, UK. Clinical Cancer Research (2004), 10(11), 3863-3870. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:420011 AN 2004:446458 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Previous studies have shown that tumor response to capecitabine strongly correlates with tumor thymidine phosphorylase (TP). The aims of our study were to (a) investigate the pharmacol. role of TP by measuring the pharmacokinetics (PK) of capecitabine in a

human bladder tumor model that was characterized by the overexpression of TP and (b) develop the use of PK measurements for capecitabine by fluorine-19 magnetic resonance spectroscopy as a noninvasive surrogate marker for detg. TP levels in tumors and for predicting tumor response to capecitabine in patients. TP overexpressing (2T10) and control tumors were grown s.c. in nude mice. Mice were given a dose of capecitabine or 5'-deoxy-5-fluorouridine (5'DFUR). 19F tumor spectra were acquired for detn. of rate consts. of capecitabine breakdown and buildup and subsequent breakdown of intermediates, 5'-deoxy-5-fluorocytidine (5'DFCR) and 5'DFUR. The rate const. of 5'DFUR breakdown was also evaluated. The rate const. of breakdown of intermediates was significantly faster in 2T10 tumors than controls ($P < 0.003$). No significant differences in the rate of capecitabine breakdown or intermediate buildup were obsd. The rate const. of 5'DFUR breakdown in the 2T10 tumors was doubled compared with controls ($P < 0.001$). This study confirmed the expected pathway of capecitabine metab. and showed that the level of TP was related to the rate of 5'DFUR conversion. Using in vivo fluorine-19 magnetic resonance spectroscopy to measure the PK of capecitabine and its intermediate metabolites in tumors may provide a noninvasive surrogate method for detg. TP levels in tumors and for predicting tumor response to capecitabine in patients.

Answer 10:

Bibliographic Information

Effects of introduction of dThdPase cDNA on sensitivity to 5'-deoxy-5-fluorouridine and tumor angiogenesis. Kim, Ryungsa; Murakami, Shigeru; Toge, Tetsuya. Department of Surgical Oncology, International Radiation Information Center, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan. International Journal of Oncology (2003), 22(4), 835-841. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 139:301452 AN 2003:271232 CAPLUS

Abstract

Human thymidine phosphorylase (dThdPase) is an angiogenic factor identical to platelet-derived endothelial cell growth factor (PD-ECGF). Thymidine phosphorylase is also a converting enzyme of the prodrug 5'-deoxy-5-fluorouridine (5'-DFUR) to 5-fluorouracil (5-FU) in tumors. To assess the role of dThdPase in targeting chemotherapy, we examd. the relationship between the expression of dThdPase and the sensitivity of 5'-DFUR in cancer cell lines, and also examd. whether transfection of dThdPase cDNA enhanced the drug-sensitivity to 5'-DFUR with or without angiogenesis in breast cancer cells. Thirteen human cancer cell lines consisting of 4 breast cancer, 6 gastric cancer, and 3 colon cancer cell lines were used. Expression of dThdPase was assessed by reverse transcriptase-polymerase chain reaction (RT-PCR) and ELISA. In vitro drug-sensitivity was assessed by MTT assay, and antitumor effect in vivo was assessed using nude mouse xenografts. Intra-tumoral microvessel d. was evaluated by immunohistochem. staining to factor VIII related antigen. Transfection of dThdPase cDNA was performed using pcDNA3 expression vector encoding its cDNA by the lipofection method. An inverse relationship between the expression of dThdPase and the IC50 values of 5'-DFUR was obsd. ($p=0.1278$, $q=-0.440$) in the 13 cancer cell lines. Transfection of dThdPase cDNA into MCF-7 breast cancer cells resulted in an approx. 2.6- and 10-fold increase of the expression of dThdPase mRNA and its enzyme activity, resp., compared to the control vector alone. The sensitivity to 5'-DFUR in the transfected cells was increased approx. 20-fold compared to the parent cells and control vector alone, and the sensitivity to 5-FU was also somewhat increased. In contrast, the sensitivity to adriamycin, CDDP, and VP-16 was not different between the transfected and control cells.

In nude mice xenografts of the transfected cells, treatment with 5'-DFUR had a significant antitumor effect compared to those of the untreated transfected cells and control vector alone treated with 5'-DFUR ($p<0.01$). Intratumoral microvessel d. in the transfected cells was not significantly increased with or without treatment with 5'-DFUR compared to control vector alone. The high expression of dThdPase was correlated with an increase in the sensitivity to 5'-DFUR in gastrointestinal and breast cancer cell lines. The introduction of dThdPase cDNA in breast cancer cells enhanced the sensitivity to 5'-DFUR without an increase of tumor angiogenesis, and targeting chemotherapy of dThdPase may be a good tumor-specific and personalized therapy for improving the poor prognosis of cancer patients who show high expressions of dThdPase.

Answer 11:

Bibliographic Information

Optimal dosing schedule in combination therapy with irinotecan and doxifluridine in a human colorectal cancer xenograft model. Yanagisawa, Mieko; Ishikawa, Tohru; Fujimoto-Ouchi, Kaori; Tanaka, Yutaka. Dept. of Product Research, Nippon Roche Research Center, Japan. Gan to Kagaku Ryoho (2003), 30(2), 223-230. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 139:254879 AN 2003:208368 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A combination therapy with CPT-11 and 5-FU/LV has been recently established as a first-line therapy for metastatic colorectal cancer. However, severe adverse effects have also been reported from this combination therapy, and a modality to reduce the adverse effects is desired. 5'-DFUR, a pro-drug of 5-FU, shows less myelotoxicity than 5-FU, and thus it may be a better partner to combine with CPT-11. However, since each drug has the possibility of inducing diarrhea, there is concern about their use in combination therapy. Therefore, in the present study, our aim was to establish an optimal schedule in murine models, which shows no increase in diarrhea but maintains potent antitumor activity. In non-tumor bearing mice, CPT-11 was given i.v. at 100 mg/kg/day q2d × 3, and 5'-DFUR was given p.o. at 172 mg/kg/day daily for 14 days. Each of these doses caused diarrhea in the single treatment. CPT-11 was administered simultaneously or sequentially with 5'-DFUR. With the simultaneously administered schedule, the diarrhea appeared stronger than that found in the CPT-11 single or in the 5'-DFUR single treatment groups. On the other hand, with the sequentially administered schedule the diarrhea was not much stronger than that found in the single agent treatment groups. When CPT-11 and 5'-DFUR administrations were sepd. by three-day intervals, the diarrhea was not augmented at all. In mice bearing human colorectal cancer COLO 205, the antitumor activity of CPT-11 in the combination with 5'-DFUR was additive in all of the examd. schedules. The efficacy in the sequential schedule was the same as in the simultaneous schedule. These results suggest that a sequential administration schedule of CPT-11 and 5'-DFUR would be more tolerable than and equally efficacious to the simultaneous administration schedule. Clin. study of this sequential administration in combination therapy is warranted.

Answer 12:

Bibliographic Information

Role of thymidine phosphorylase in an in vitro model of human bladder cancer invasion. Jones, Adam; Fujiyama, Chisato; Turner, Kevin; Cranston, David; Williams, Kaye; Stratford, Ian; Bicknell, Roy; Harris, Adrian L. Imperial Cancer Research Fund, John Radcliffe Hospital, University of Oxford Institute of Molecular Medicine, Headington, UK. Journal of Urology (Hagerstown, MD, United States) (2002), 167(3), 1482-1486. Publisher: Lippincott Williams & Wilkins, CODEN: JOURAA ISSN: 0022-5347. Journal written in English. CAN 137:123104 AN 2002:204502 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

It has been previously demonstrated that the angiogenic factor thymidine phosphorylase is elevated significantly in invasive bladder cancer. The authors report that it is not merely an incidental finding. Thymidine phosphorylase has a functional role in bladder cancer invasion. The superficial bladder cancer cell line RT112 was transfected by retroviral techniques to generate the RT112-TP clone that expressed significantly elevated levels of thymidine phosphorylase, comparable to those of invasive human bladder cancers. The empty vector control RT112-EV was generated for comparison. Growth of these transfectants was examd. using a new in vitro model of bladder cancer invasion based on de-epithelialized rat bladder and by assessing growth as xenografts in nude mice. The effect of 5'-deoxy-5-fluorouridine, a prodrug activated by TP to produce 5-fluorouracil, was also examd. RT112-TP high thymidine phosphorylase expressing cells invaded into the stroma of the in vitro model but wild-type RT112 and RT112-EV cells did not. This invasion was abolished by 5'-deoxy-5-fluorouridine. Invasion correlated with thymidine phosphorylase expression on immunohistochem. testing. There was also a significantly greater xenograft growth rate for RT112-TP than for RT112-EV, confirming the malignant growth advantage conferred by thymidine phosphorylase. The authors demonstrated that thymidine phosphorylase may have a functional role in bladder cancer invasion and the apparent advantage of thymidine phosphorylase expression to tumor cells can be exploited by therapies that utilize prodrugs such as 5'-deoxy-5-fluorouridine, which is activated by thymidine phosphorylase and inhibited invasion in the authors' model.

Answer 13:

Bibliographic Information

Investigation of 5-FU disposition after oral administration of capecitabine, a triple-prodrug of 5-FU, using a physiologically based pharmacokinetic model in a human cancer xenograft model: comparison of the simulated 5-FU exposures in the tumor tissue between human and xenograft model. Tsukamoto, Yuko; Kato, Yukio; Ura, Masako; Horii, Ikuo; Ishikawa, Tohru; Ishitsuka, Hideo; Sugiyama, Yuichi. Nippon Roche Research Centre, Kanagawa, Japan. Biopharmaceutics & Drug Disposition (2001), 22(1), 1-14. Publisher: John Wiley & Sons Ltd., CODEN: BDDID8 ISSN: 0142-2782. Journal written in English. CAN 136:210013 AN 2001:887500 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The nonlinear pharmacokinetics of capecitabine, a triple prodrug of 5-FU preferentially activated in tumor tissues, was investigated in human cancer xenograft models. A physiol. based pharmacokinetic (PBPK) model integrating the activation process of capecitabine to 5-FU and 5-FU elimination was constructed to describe the concn./time profiles of capecitabine and its three metabolites, including 5-FU, in blood and organs. All the biochem. parameters (enzyme kinetic parameters, plasma protein binding and tissue binding of capecitabine and its metabolites) integrated in this model were measured in vitro. The simulated curves for the blood and tumor concns. of capecitabine and its metabolites can basically describe the obsd. values. A simple prodrug of 5-FU, doxifluridine, is known to be activated to 5-FU to some extent in the gastrointestinal (GI) tract, causing diarrhea, which is the dose limiting side effect of doxifluridine. Consequently, the therapeutic index (the ratio of 5-FU AUC in the tumor to that in GI) after the administration of ED capecitabine was predicted by this PBPK model and five times and 3000 times greater than that of doxifluridine and 5-FU, resp. This was compatible with the previous result for the difference in the ratio of the toxic dose to the min. ED between capecitabine and doxifluridine, suggesting that 5-FU preferentially accumulates in tumor tissue after oral administration of capecitabine compared with the other drugs (doxifluridine and 5-FU). The 5-FU AUC in tumor tissue of human cancer xenograft models at the min. ED was comparable with those estd. for humans at the clin. dose. In addn., the predicted therapeutic indexes at the resp. doses were correlated well between humans and mice (xenograft model). These results suggest that the 5-FU AUC in human tumor tissue at its clin. ED can be predicted based on the PBPK model inasmuch as the 5-FU AUC in a human cancer xenograft model at its ED may be measured or simulated.

Answer 14:

Bibliographic Information

Combined effects of docetaxel and fluoropyrimidines on tumor growth and expression of interleukin-6 and thymidine phosphorylase in breast cancer xenografts. Yamamoto, Shigeru; Kurebayashi, Junichi; Kurosumi, Masafumi; Kunisue, Hironori; Otsuki, Takemi; Tanaka, Katsuhiro; Sonoo, Hiroshi. Department of Breast and Thyroid Surgery, Kawasaki Medical School, Kurashiki, Okayama, Japan. Cancer Chemotherapy and Pharmacology (2001), 48(4), 283-288. Publisher: Springer-Verlag, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 137:87924 AN 2001:695783 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Although several combination treatments with docetaxel and other antitumor agents have been tested in exptl. and clin. studies, their synergistic effects are still ill-defined. The degree of synergism between docetaxel and two oral fluoropyrimidines, Tegafur and 5'-deoxy-5-fluorouridine (5'-dFUrd), was investigated in the KPL-4 human breast cancer xenograft model. Because this KPL-4 cell line secretes interleukin-6 (IL-6) and induces cachexia, the effects of the combined treatment on serum IL-6 levels and cachectic markers were investigated. In addn., the expression levels of thymidine phosphorylase (dThdPase), a key enzyme for converting 5'-dFUrd to 5-fluorouracil, were detd. Female nude mice bearing KPL-4 tumors were treated orally with 5'-dFUrd (60 mg/kg, five times a week) or Tegafur (100 mg/kg, five times a week) and by i.p. injection of docetaxel (5 or 10 mg/kg, once a week). Although docetaxel (5 mg/kg) alone did not decrease either tumor growth or serum IL-6 levels, docetaxel (5 mg/kg) plus 5'-dFUrd or Tegafur enhanced tumor growth inhibition and decreased serum IL-6 levels more than 5'-dFUrd or Tegafur alone. Docetaxel (5 mg/kg) alone slightly increased the percentage of dThdPase-pos. tumor cells, but the combined treatment with docetaxel plus 5'-dFUrd or Tegafur significantly decreased the percentage of dThdPase-pos. cells in the KPL-4 tumors. These findings indicate that docetaxel may stimulate dThdPase expression in tumor tissues and may enhance the antitumor activity of oral fluoropyrimidines. In addn., combined treatment with

docetaxel and oral fluoropyrimidines may decrease serum IL-6 levels and may ameliorate IL-6-induced cancer cachexia.

Answer 15:

Bibliographic Information

Schedule dependency of antitumor activity in combination therapy with capecitabine/5'-deoxy-5-fluorouridine, and docetaxel in breast cancer models. Fujimoto-Ouchi, Kaori; Tanaka, Yutaka; Tominaga, Takeshi. Oncology, Nippon Roche Research Center, Kanagawa, Japan. Clinical Cancer Research (2001), 7(4), 1079-1086. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 136:48073 AN 2001:363667 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Docetaxel and capecitabine are being prescribed for the treatment of breast cancer. In this study, the authors tried to identify the optimal administration schedule in combination therapy with these anticancer drugs in human cancer xenograft models. Capecitabine was given p.o. daily for 2 wk (days 1-14), whereas docetaxel was given i.v. on day 1, day 8, or day 15 in a 3-wk regimen to the mice bearing MX-1 human breast cancer xenograft. The combination showed better antitumor efficacy than the monotherapy of either agent in either dosing regimen. However, the most potent and synergistic activity was obsd. when docetaxel was given on day 8. This potent effect appears to be characteristic of the combination of docetaxel with capecitabine or its intermediate metabolite 5'-deoxy-5-fluorouridine (doxifluridine: 5'-dFUrd). Docetaxel given on day 8 showed a potent effect in combination with 5'-dFUrd, but a much weaker effect was obsd. in combination with 5-fluorouracil or UFT, a fixed combination of tegafur and uracil. Better efficacy was also obsd. in the MAXF401 human breast cancer xenograft and in the mouse A755 mammary tumor when docetaxel was given at the middle of the capecitabine or 5'-dFUrd treatment rather than other dosing regimens. In contrast, the efficacy in WiDr human colon cancer xenograft was somewhat better when docetaxel was given on day 1. One possible explanation for the synergy is that docetaxel up-regulates tumor levels of thymidine phosphorylase, the enzyme essential for the activation of capecitabine and 5'-dFUrd to 5-fluorouracil. In fact, docetaxel up-regulated the thymidine phosphorylase levels 4.8- and 1.9-fold in the WiDr and MX-1 models, resp. However, it did not up-regulate in the MAXF401 and A755 models in which a potent combination effect was obsd. as well. Other mechanisms, particularly those for the synergy with docetaxel given at the middle during capecitabine/5'-dFUrd administration, would also exist. Based on these observations, clin.

studies on the day 8 combination regimen with docetaxel and capecitabine/5'-dFUrd are warranted.

Answer 16:

Bibliographic Information

Effect of a fluorinated pyrimidine on cachexia and tumour growth in murine cachexia models. Relationship with a proteolysis inducing factor. Hussey, H. J.; Todorov, P. T.; Field, W. N.; Inagaki, N.; Tanaka, Y.; Ishitsuka, H.; Tisdale, M. J. Pharmaceutical Sciences Research Institute, Aston University, Birmingham, UK. British Journal of Cancer (2000), 83(1), 56-62. Publisher: Harcourt Publishers Ltd., CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 133:344251 AN 2000:497338 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The fluorinated pyrimidine nucleoside, 5'-deoxy-5-fluorouridine (5'-dFUrd) was shown to effectively attenuate the progress of cachexia in the murine adenocarcinomas MAC16 and colon 26 as well as in the human uterine cervical carcinoma xenograft, Yumoto. Although concomitant inhibition of tumor growth was obsd. in all 3 models this was not sufficient to account for the preservation of body wt. An attempt was made to correlate the anti-cachectic activity of 5'-dFUrd with the presence of a tumor produced proteolysis-inducing factor (PIF), thought to be responsible for the development of cachexia in the MAC16 model. Two variants of colon 26 adenocarcinoma were employed, clone 20 which produces profound cachexia, and clone 5 which produces no change in body wt. in recipient animals. Mice bearing the colon 26, clone 20 variant showed evidence for the presence of PIF in tumor, serum, and urine, while there was no evidence for the presence of PIF in tumor or body fluids of mice bearing the clone 5 tumors. Treatment of animals

bearing the clone 20 variant with 5'-dF Urd led to the disappearance of PIF from the tumor, serum and urine concomitant with the attenuation of the development of cachexia. The human cervical carcinoma, Yumoto, which also induced cachexia in recipient animals, showed expression of PIF in tumor, serum and urine in control and vehicle-treated mice, but was absent in mice treated with 5'-dFUrd. Thus in these exptl. models cachexia appears to be correlated with the presence of PIF.

Answer 17:

Bibliographic Information

Evaluation of antitumor activity of etoposide administered orally for 21 consecutive days against human uterine cancer subcutaneous and/or orthotopic xenografts in nude mice. Matsumoto, Sayuri; Mashiba, Hiroko; Okamoto, Kazuya; Ekimoto, Hisao. Anticancer Drugs Dept., Research & Development Division, Pharmaceutical Group, Nippon Kayaku Co., Ltd, Japan. Gan to Kagaku Ryoho (1999), 26(9), 1313-1320. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 132:117203 AN 1999:634564 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor activity of etoposide (ETP) against human uterine cancer cell lines were investigated in vitro and in vivo. The cytotoxic activity of ETP against HeLa S3, a human cervical cancer cell line, depended on exposure time. The survival rate with 24 h prolonged exposure was reduced to about 1/200 that with 6 h exposure. The time dependency of antitumor activity of ETP against HeLa S3 s.c. transplanted in nude mice was studied. The effect of 21 or 28 consecutive days oral administration was greater than that of 5 or 14 consecutive days. Furthermore, a longer administration schedule was less toxic. The antitumor activity of ETP administered orally for 21 consecutive days was compared with that of CDDP, CPT-11 and 5'-DFUR using both human uterine cancer cell lines (TCO-1, SIHA, UCC08JCK) transplanted s.c. in nude mice and human uterine cancer cell lines (HeLa S3, UCC08JCK) transplanted into the uterus of nude mice. ETP showed the same antitumor activity as CPT-11 and 5'-DFUR against TCO-1 and UCC08JCK, human uterine cancer cell lines transplanted s.c. in nude mice. ETP also showed anticancer activity against two cell lines transplanted into the uterus. The growth inhibition caused by ETP administered orally at 50 mg/kg against HeLa S3 transplanted s.c. was 36.7% while that against the same cell line transplanted into the uterus was 58.5%. 5'-DFUR also showed the same antitumor activity as ETP. These results suggest that long term oral administration of ETP is clin. useful for cervical cancer patients.

Answer 18:

Bibliographic Information

Induction of thymidine phosphorylase expression and enhancement of efficacy of capecitabine or 5'-deoxy-5-fluorouridine by cyclophosphamide in mammary tumor models. Endo, Mika; Shinbori, Noriko; Fukase, Yu; Sawada, Noriaki; Ishikawa, Tohru; Ishitsuka, Hideo; Tanaka, Yutaka. Cytostatics Group, Nippon Roche Research Center, Kanagawa, Japan. International Journal of Cancer (1999), 83(1), 127-134. Publisher: Wiley-Liss, Inc., CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 132:117196 AN 1999:599453 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Thymidine phosphorylase (dThdPase) is an essential enzyme for the activation of the oral cytostatic drugs capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine, Xeloda) and its intermediate metabolite doxifluridine [5'-deoxy-5-fluorouridine (5'-dFUrd, Furtulon)] to 5-fluorouracil (5-FUra) in tumors. In a previous study, we found that several cytostatics were able to up-regulate tumor levels of dThdPase in a human colon cancer xenograft model. In the present study, we confirmed that the administration of cytostatics used for breast cancer treatment, such as taxanes and cyclophosphamide (CPA), up-regulated the tumor level of dThdPase in mammary tumor models as well. Because the dThdPase up-regulation was obsd. even when CPA was given orally, we investigated further the usefulness of combination therapy with the 2 oral drugs, 5'-dFUrd/capecitabine and CPA in mammary tumor models. Daily oral administration of CPA up-regulated human dThdPase levels in the tumor tissue of mice bearing a human mammary tumor xenograft, MX-1, whereas in the small intestine and liver, it did not affect levels of pyrimidine nucleoside phosphorylases (PyNPase) including dThdPase and uridine phosphorylase. The preferential up-regulation of PyNPase activity in the

tumor by CPA administration was also confirmed in mice bearing a syngeneic murine mammary adenocarcinoma, A755. In both models, combination therapy of 5'-dFUrd/capecitabine with CPA showed synergistic antitumor activity, without significant potentiation of toxicity. In contrast, treatment with CPA and either 5-FUra or UFT (a mixt. of tegafur and uracil) in combination showed only additive activity. Our results suggest that CPA and capecitabine/5'-dFUrd, both available for oral administration, would be good partners, and that clin. trials with this drug combination against breast cancer are warranted.

Answer 19:

Bibliographic Information

Antitumor activities of a novel fluoropyrimidine, N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine (Capecitabine). Ishikawa, Tohru; Fukase, Yu; Yamamoto, Taeko; Sekiguchi, Fumiko; Ishitsuka, Hideo. Cytostatics Group, Nippon Roche Research Center, Kanagawa, Japan. Biological & Pharmaceutical Bulletin (1998), 21(7), 713-717. Publisher: Pharmaceutical Society of Japan, CODEN: BPBLEO ISSN: 0918-6158. Journal written in English. CAN 129:197704 AN 1998:478091 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine) is a novel fluoropyrimidine carbamate that was synthesized for the purpose of finding antitumor drugs with improved safety and efficacy profiles compared with those of 5-fluorouracil (5-FUra) and doxifluridine (5'-deoxy-5-fluorouridine, 5'-dFUrd). The present study compared the antitumor activities of the compd. with those of other fluoropyrimidines in 12 human cancer xenograft models and their antimetastatic activities in murine tumor models. The antitumor efficacy of capecitabine was greater than those of 5'-dFUrd, UFT (a mixt. of Tegafur and uracil) and 5-FUra. Capecitabine was also much safer, particularly much less toxic to the intestinal tract, than the other compds., indicating higher therapeutic indexes. The therapeutic indexes of capecitabine, 5'-dFUrd and 5-FUra were >40, >20 and 2.0 against the human CXF280 colon cancer xenograft, the most sensitive line to the fluoropyrimidines so far tested, and 5.1, 1.5, and <1.5 against the human HCT116 colon cancer xenograft with ordinary sensitivity, resp. In addn., capecitabine, as well as 5'-dFUrd, selectively suppressed the spontaneous metastasis of mouse Lewis lung carcinoma in mice at extremely low doses, 32-64 fold lower than their min. ED (MED) against the primary tumor growth. Capecitabine was even more antimetastatic than 5'-dFUrd. These results indicate that capecitabine has high therapeutic potential.

Answer 20:

Bibliographic Information

Interferon alpha and 5'-deoxy-5-fluorouridine in colon cancer: effects as single agents and in combination on growth of xenograft tumors. Laurent, P.L.; Tevaearai, H.T.; Eliason, J.F.; Givel, J.-C.; Odartchenko, N. Swiss Institute for Experimental Cancer Research, Epalinges, Switz. Eur. J. Cancer, Part A (1994), 30A(12), 1859-65. CODEN: EJCTEA Journal written in English. CAN 122:158239 AN 1995:368337 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Interferon-α (IFN-α) enhances the activity of the 5-fluorouracil (5-FU) prodrug 5'-deoxy-5-fluorouridine (5'-dFUrd) in colorectal cancer cells in vitro by upregulating the enzyme pyrimidine nucleoside phosphorylase (PNPase), which is responsible for converting 5'-dFUrd to 5-FU. The authors examd. whether such enhancement also occurs in vivo using human colorectal xenografts in nude mice. The Co-115 line has high basal levels of PNPase and the enzyme level was increased in tumors from mice treated for 3 wk with 50,000 IU/day (5 days/wk) of IFN-αA/D. The prodrug 5'-dFUrd (200 mg/day, 5 days/wk) had a much greater antitumor activity than 5-FU had when it was used at an approx. equitoxic dose (20 mg/day, 5 days/wk). However, because of the high activity of 5'-dFUrd as a single agent, no enhancement by IFN-αA/D was obsd. Studies on xenografts of WiDr cells indicated that this line is much less sensitive to 5'-dFUrd. However, treatment of animals with IFN-αA/D at doses of 75,000 IU/day or 150,000 IU/day resulted in inhibition of WiDr tumor growth. Combination treatment with 75 mg/kg/day or 150 mg/kg/day of 5'-dFUrd resulted in enhanced antitumor activity, particularly at the higher dose of IFN-αA/D. Synergy of this drug combination was confirmed by isobologram anal. Anal. of PNPase

levels in WiDr tumors, excised from mice treated with IFN-αA/D, demonstrated that the enzyme activity was increased by IFN-α in a dose-dependent manner. Slight increases were also seen in normal liver and intestine from the same animals. Thus, modulation of converting enzymes for anticancer prodrugs by cytokines could be a novel therapeutic strategy for combination therapy of colorectal cancer.

Answer 21:

Bibliographic Information

Predictability of clinical response to anticancer agents in human cancer xenografts. Tsukamoto, Fumine. Med. Sch., Osaka Univ., Suita, Japan. Osaka Daigaku Igaku Zasshi (1994), 46(4), 251-61. CODEN: ODIZAK ISSN: 0369-710X. Journal written in Japanese. CAN 121:124753 AN 1994:524753 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Nude mouse transplanted human tumors retained original sensitivity to antitumor drugs, and was useful in secondary screening for the sensitivity to tumor chemotherapy. Fresh tumor tissues were transplanted and maintained in nude mice in 77 cases (tried: 247 cases), and sensitivity of the transplanted tumors to chemotherapy was compared between human therapy and in nude mice using regimen used clin. in 17 cases with 21 expts. (stomach, breast, colon, pancreas, esophagus. melanoma). Tested drugs were adriamycin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, doxifluoridine, epirubicin, 5-fluorouracil, M-83 (a mitomycin C deriv.), mitomycin C, tegafur, and UFT. Chemotherapy in nude mice was effective in 6 expts., which coincided with clin. results in 5 cases. The ineffective 15 cases in nude mice coincided with the clin. results in all cases.

Answer 22:

Bibliographic Information

Antitumor activity of 5'-deoxy-5-fluorouridine in human digestive organ cancer xenografts and pyrimidine nucleoside phosphorylase activity in normal and neoplastic tissues from human digestive organs. Nio, Yoshinori; Kimura, Hiroko; Tsubono, Michihiko; Tseng, Chen-Chiu; Kawabata, Kazuya; Masai, Yoshikazu; Hayashi, Hitoshi; Meyer, Carole; Fukumoto, Manabu; Tobe, Takayoshi. 1st Dep. Surg., Kyoto Univ. Fac. Med., Kyoto, Japan. Anticancer Research (1992), 12(4), 1141-6. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 121:26399 AN 1994:426399 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

5'-Deoxy-5-fluorouridine (5'-DFUR) is believed to be metabolized to 5-fluorouracil (5-FU) by pyrimidine nucleoside phosphorylase (PyNPase). PyNPase activity is reported to be higher in neoplastic tissues than in normal tissues, and this has been proposed as an explanation for the selective cytotoxicity of 5'-DFUR against tumors. In the present study, PyNPase activity was measured in 95 neoplastic and normal specimens from human digestive organ tissues. In specimens from the esophagus, stomach, intestine and pancreas, PyNPase activity was higher in neoplastic tissues than in normal tissues. However, PyNPase activity in non-malignant liver tissues, esp. cirrhotic liver tissues, was much higher than in the normal tissues of the other digestive organs. PyNPase activity in non-malignant liver tissues was as high as in primary liver tumors, and PyNPase activity in metastatic liver tumors was lower than in primary tumors and non-malignant cirrhotic tissues. The in vivo antitumor activities of oral 5'-DFUR and i.v. 5-FU were also assessed in 6 human digestive organ cancer xenograft lines transplanted s.c. in nude mice, and the relationship between the in vivo antitumor effects of 5'-DFUR and PyNPase activity in the tumors was assessed. However, there was no statistically significant correlation between them. Although the in vivo antitumor effect of i.v. 5-FU correlated significantly with the in vitro sensitivity of the tumors to 5-FU (assessed by DNA synthesis inhibition assay), the in vivo effects of 5'-DFUR did not correlate with the in vitro sensitivity to 5-FU. It is suggested that: (a) the liver may be the major site for metabolizing 5'-DFUR to 5-FU, and (b) measuring PyNPase activity in the tumor may not be a useful indicator for chemotherapy with 5'-DFUR.

Answer 23:

Bibliographic Information

A comparative study of the antitumor activities of 5'-deoxy-5-fluorouridine and its prodrug trimethoxy benzoyl-5'-deoxy-5-fluorocytidine (Ro09-1390) on human digestive organ cancer xenograft lines transplanted into nude mice. Nio, Yoshinori; Kimura, Hiroko; Tsubono, Michihiko; Tseng, Chen Chiu; Kawabata, Kazuya; Masai, Yoshikazu; Hayashi, Hitoshi; Araya, Shinichi; Meyer, Carole; Fukumoto, Manabu. Fac. Med., Kyoto Univ., Kyoto, Japan. Anti-Cancer Drugs (1992), 3(4), 387-93. CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 118:15930 AN 1993:15930 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

5'-Deoxy-5-fluorouridine (5'-DFUR) is one of the oral fluoropyrimidines widely used in the treatment of gastric, colorectal and breast cancers in Japan. 5'-DFUR is converted to 5-fluorouracil by pyrimidine nucleoside phosphorylase in the tumor. 5'-DFUR has toxic effects on the intestine and may cause severe diarrhea. Trimethoxybenzoyl-5'-deoxy-5-fluorocytidine (Ro09 1390) is a prodrug of 5'-DFUR, which was developed to reduce the intestinal toxicity of 5'-DFUR. The present study was designed to assess the antitumor activity and spectrum of Ro09-1390, and to compare its efficacy with that of 5'-DFUR. Six digestive organ cancer xenograft lines (two gastric, one esophageal, one colorectal, one gall bladder and one bile duct cancers) were s.c. transplanted into nude mice. The agents were orally administered daily for 14 days at doses of 0.08-0.64 mmol/kg (1-8 times the maximal clin. dose of 5'-DFUR). Both 5'-DFUR and Ro09-1390 significantly inhibited the growth of two gastric cancer lines, and the IC50's for Ro09-1390 in both lines were lower than the resp. values for 5'-DFUR. The esophageal, colorectal, gall bladder and bile duct cancer lines, however, were resistant to both agents. 5'-DFUR at 0.64 mmol/kg significantly inhibited the growth of these cancers, but with high mortality, and most mice receiving this dose died within 14 days after the start of therapy, suffering from severe diarrhea and body wt. loss. Ro09-1390 at the same dose resulted in low mortality, but evidenced similarly low antitumor activity. These results suggest that Ro09-1390 may be a more beneficial antitumor fluoropyrimidine, at least in the treatment of gastric cancer, than 5'-DFUR.

Answer 24:

Bibliographic Information

Comparative studies on the antitumor activity of fluorinated pyrimidine derivatives against human bladder, cervical and ovarian cancer xenografts in nude mice. Miwa, Masanori; Sekiguchi, Fumiko; Akaza, Hideyuki; Tokita, Hisashi; Nitta, Kazuo; Adachi, Shigemi; Kanazawa, Kohji; Ishitsuka, Hideo. Dep. Oncol. Immunol., Nippon Roche Res. Cent., Kamakura, Japan. Gan to Kagaku Ryoho (1991), 18(10), 1579-86. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 116:333 AN 1992:333 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Fluorinated pyrimidines given orally were examd. for their antitumor activity with 11 human cancer xenograft models (4 bladder, 4 cervical and 3 ovarian cancers). The drugs were evaluated to be effective when they inhibited tumor growth over 58%. UFT was not effective against the 11 cancer xenografts tested. 5-Fluorouracil (5-FU) was effective against only 1 bladder cancer xenograft among 6 cancer xenografts tested. On the other hand, 5'-deoxy-5-fluorouridine (5'-DFUR) was effective against 1 bladder, 3 cervical and 1 ovarian cancer xenografts. The antitumor activity of 5'-DFUR was correlated with the enzyme activity of pyrimidine nucleoside phosphorylase, which is an essential enzyme for phosphorolysis of 5'-DFUR to 5-FU.

Answer 25:

Bibliographic Information

Predictability of preclinical evaluation of anticancer drugs by human gastrointestinal cancer-nude mouse panel. Fujita, Masahide; Fujita, Fumiko; Sakamoto, Yasuo; Sugimoto, Takuji; Shimozuma, Kojiro; Taguchi, Tetsuo. Res. Inst. Microb. Dis., Osaka Univ., Suita, Japan. Gan to Kagaku Ryoho (1991), 18(9), 1429-37. CODEN: GTKRDX ISSN: 0385-0684. Journal written in

Japanese. CAN 115:269825 AN 1991:669825 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The predictability of clin. responses to anticancer agents was studied using a human cancer-nude mouse panel. The human cancer lines used were 12 gastric, 4 colorectal, 3 breast, 2 pancreatic cancers and 1 melanoma xenografted into BALB/c athymic nude mice. Treatment was conducted daily 25 times for antimetabolites, and intermittently 5 times once or twice a week for other drugs. The dosage of each drug was the maximal tolerated dose predetd. for the treatment and schedule. Four weeks after the initiation of treatment, the therapeutic effect was evaluated by the tumor growth inhibition rate (IR) based on the mean tumor wt. When the IR was >58%, the drug was evaluated as effective. The clin. response rate of each drug was referred from the result of a phase II study. Direct comparison of antitumor effects on 16 tumor xenografts with responses to the corresponding clin. therapy of each donor patient revealed a fairly high accordance rate (94%). To elucidate the value of human cancer-nude mouse panel as a preclin. secondary screening, the response rates to 8 anticancer drugs used in 15 cancer xenografts were compared with the cumulative clin. data available for each drug. Generally, the response rates of the human cancer xenografts to the drugs showed fairly good correlations with the cumulative clin. response rates to the corresponding drugs in the same organs. Using this panel, preclin. examns. of 6 new agents under development, including 254-S and 2 cisplatin derivs., were performed in order to collect clin. data.

Answer 26:

Bibliographic Information

Therapeutic strategies for 5-fluorouracil-leucovorin based upon cellular metabolic characteristics in human colon adenocarcinoma xenografts. Houghton, J. A.; Williams, L. G.; Cheshire, P. J.; Houghton, P. J.; De Graaf, S. S. N. Dep. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. Editor(s): Curtius, Hans-Christoph; Ghisla, Sandro; Blau, Nenad. Chem. Biol. Pteridines, 1989 Proc. Int. Symp. Pteridines Folic Acid Deriv., 9th (1990), Meeting Date 1989, 1203-8. Publisher: de Gruyter, Berlin, Fed. Rep. Ger CODEN: 57FTAQ Conference written in English. CAN 115:149839 AN 1991:549839 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In human colon adenocarcinoma xenografts in mice, [6R,S]leucovorin (I) increased the pools of reduced folates, an effect that was reversed upon stopping its infusion. I also increased the thymidylate synthase inhibition by 5-fluorouracil (II). The results are discussed in relation to the antitumor activity of I plus II.

Answer 27:

Bibliographic Information

Effects of 5'-deoxy-5-fluorouridine as single agent or combination chemotherapy in human cancers xenografted into nude mice. Fujita, M.; Fujita, F.; Taguchi, T. Res. Inst. Microb. Dis., Osaka Univ., Suita, Japan. Journal of International Medical Research (1988), 16(Suppl. 2), 9B-12B, 36B-39B. CODEN: JIMRBV ISSN: 0300-0605. Journal written in English. CAN 110:412 AN 1989:412 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Oral administration of 5'-deoxy-5-fluorouridine (5'-DFUR) effectively inhibited tumor growth in 11/15 (73%) cancer lines: 5/7 (71%) gastric cancers; 2/3 (67%) colorectal cancers; 3/3 (100%) breast cancers; and 1/2 (50%) pancreatic cancers. In some cases, shrinkage of tumors was noted without the occurrence of noticeable side-effects. Growth inhibition of 80% was achieved in all but one (11/12, 92%) cancer line following combination chemotherapy with 5'-DFUR plus mitomycin C, at the highest dosage levels, compared with 5/12 (42%) tumors which responded to single drug therapy at the highest dosage level. Moreover, tumor shrinkage was obsd. in 7/12 (58%) tumor lines following 5'-DFUR plus mitomycin C combination therapy compared with 3/12 (25%) after single drug therapy. The synergistic effects of combination chemotherapy with 5'-DFUR plus vindesine, cisplatin, and methotrexate is reported.

Answer 28:

Bibliographic Information

Combined effects of interferon α-A/D with fluoropyrimidine derivatives in subrenal capsule assay. Nishiyama, Masahiko; Takagami, Shinichi; Kirihara, Yoshimasa; Saeki, Toshiaki; Niimi, Ken; Kim, Ryungsa; Jinushi, Kazuto; Toge, Tetsuya; Niimoto, Minoru; Hattori, Takao. Res. Inst. Nucl. Med. Biol., Hiroshima Univ., Hiroshima, Japan. Gan to Kagaku Ryoho (1988), 15(8), 2285-90. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 109:204561 AN 1988:604561 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Synergistic, additive, or subadditive antitumor effects were obsd. following the combined administration of interferon α-A/D with fluoropyrimidine derivs. (i.e., 5-FU, tegafur, and 5'-deoxy-5-fluorouridine, UFT, and 1-hexylcarbamoyl-5-fluorouracil) to athymic mice bearing human tumor xenografts (H-111 and SH-10 gastric cancers and CH-5 colon cancer). The combinations were not effective against CH-4 colon cancer of human.

Answer 29:

Bibliographic Information

Combination chemotherapy of human gastrointestinal and breast cancer xenografts in nude mice with 5'-deoxy-5-fluorouridine and mitomycin C. Fujita, Fumiko; Fujita, Masahide; Shimozuma, Kojiro; Taguchi, Tetsuo. Res. Inst. Microb. Dis., Osaka Univ., Osaka, Japan. Nippon Gan Chiryo Gakkaishi (1986), 21(7), 1386-96. CODEN: NGCJAK ISSN: 0021-4671. Journal written in Japanese. CAN 107:126609 AN 1987:526609 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects of exptl. combination chemotherapy with 5'-deoxy-5-fluorouridine (5'-DFUR) and mitomycin C (MMC) against 13 human gatrointestinal and breast cancer xenografts in BALB/c nude mice were evaluated in comparison with each of the single agent chemotherapy. With single agent therapy, remarkable suppression with I.R (inhibition rate) ≥80% was obtained in 5 lines in each drug. In contrast, combined therapy achieved I.R (≥80% in every line except one (92%). Besides, tumor shrinkage was obsd. in 7 lines in combination chemotherapy compared to 3 each in single agent therapies. Consequently, synergistic effects were seen in 8 (62%) of 13 lines examd. Side effects in combination therapy were equiv. to or slightly less than the corresponding single agent therapy.

Answer 30:

Bibliographic Information

Effects of alternating chemotherapy with 2 non-cross-resistant drug combinations on human alimentary and breast cancer xenografts in nude mice. Fujita, Fumiko; Fujita, Masahide; Yamauchi, Teruo; Sakamoto, Yasuo; Shimozuma, Kojiro; Inaba, Hiizu; Taguchi, Tetsuo. Res. Inst. Microb. Dis., Osaka Univ., Osaka, Japan. Gan to Kagaku Ryoho (1987), 14(5, Pt. 1), 1297-304. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 107:126598 AN 1987:526598 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effectiveness of alternating chemotherapy with the combination regimens I [mitomycin C (MMC) and 5'-deoxy-5-fluorouridine (5'-DFUR)] and II [cisplatin(CDDP), 5'-DFUR, and vindesine(VDS)] was evaluated using 3 lines of cancer xenografts (breast, colon, and pancreas) in nude mice with special emphasis on relapse-free survival. Results showed that cyclic delivery of two

non-cross-resistant drug combinations with optimal treatment doses and timing prevented toxic effects and induced long-term survival without relapse.

Answer 31:

Bibliographic Information

Combination chemotherapy with three or four drugs on human breast and gastrointestinal cancer xenografts in nude mice (II). Fujita, Fumiko; Fujita, Masahide; Sakamoto, Yasuo; Shimozuma, Kojiro; Inaba, Hiizu; Taguchi, Tetsuo. Res. Inst. Microb., Osaka Univ., Osaka, Japan. Gan to Kagaku Ryoho (1987), 14(5, Pt. 1), 1252-9. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 107:126597 AN 1987:526597 CAPLUS

Abstract

Combined applications of 4 drugs, vindesine (VDS), methotrexate (MTX), cisplatin (CDDP) and 5'-DFUR (5'-deoxy-5-fluorouridine) against 3 lines of human breast cancer (H-62, H-31, H-71), and one line each of gastric cancer (H-55) and colon cancer (H-110) xenografted into nude mice were evaluated in comparison with CAF (cyclophosphamide, adriamycin and 5-fluorouracil (5-FU) therapy which is commonly used for breast cancer. Combination therapy with 3 drugs (VDS, CDDP and 5'-DFUR) or 4 drugs (VDS, CDP, MTX and 5'-DFUR) achieved a marked effect with tumor shrinkage in 3 lines of tumors (H-55, H-31 and H-62). Moreover, remarkable effects were shown even in the other 2 lines which were insensitive to every single-agent therapy. A synergistic effect was obtained in 3 of the 5 lines examd. These combination therapies were histol. superior to therapies employing single-drug or CAF therapy. The side effects for combination of these 3 or 4 drugs evaluated by body wt. loss were transient and equiv. to maximal dose of VDS or CDCP.

Answer 32:

Bibliographic Information

Evaluation by multiple regression analysis of factors influencing the chemosensitivity of human tumors xenografted into nude mice. Fujita, Fumiko; Fujita, Masahide; Hirai, Toshihiro; Taguchi, Tetsuo. Res. Inst. Microb. Dis., Osaka Univ., Osaka, Japan. Gan to Kagaku Ryoho (1987), 14(3, Pt. 1), 618-25. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 107:17103 AN 1987:417103 CAPLUS

Abstract

The chemosensitivity of human cancer lines is thought to be a result of contributions of various interacting factors. Multiple regression analyses were performed in order to clarify the weighting of factors responsible for the chemosensitivity of 15 human cancers xenografted into nude mice. Inhibition rates of 11 anticancer agents, predetd. sep. for each cancer line, were used as the criterion variables. As the explanatory variables, 9 parameters characteristic of each cancer or cancer-bearing mouse were selected as follows: grade of differentiation, vascularity, percentage of necrosis, vol. doubling time, labeling index, lactic dehydrogenase (LDH) activity, tissue/serum LDH ratio, thymidine phosphorylase activity, and serum carcinoembryonic antigen. By applying this anal. with stepwise deletion, the estd. multiple regression equations for drug sensitivity were detd. for each drug. Although all equations were composed of different factors and their partial inhibition coeffs. varied from drug to drug, the equations for analogous drugs such as FT-207 and UFT, or mitomycin C and M-83, had similar factors. The equations for M-83, ACNU, and adriamycin consisted of a no. of parameters with a sufficiently high coeff. of detn. of 80%. Even for drugs such as methotrexate, that showed no significant factor upon simple correlation anal., an equation with 7 factors revealed a coeff. of detn. of 0.83. The estd. values of effectiveness of these drugs showed marked coincidence with the actual values. For some drugs, the in vivo mode of action was inferred through this anal.

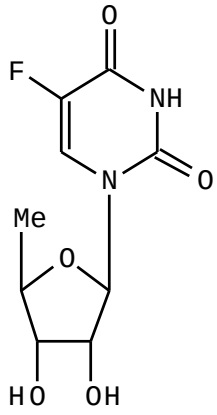
Answer 33:

Bibliographic Information

Antitumor activity of a new fluoropyrimidine derivative, 5'-deoxy-5-fluorouridine, against murine and human experimental tumors. Fujimoto, Shuichi; Wang, Yi; Inoue, Katsuhiro; Ogawa, Makoto. Cancer Chemother. Cent., Jpn. Found. Cancer Res., Tokyo, Japan. Japanese Journal of Cancer Research (1985), 76(7), 644-50. CODEN: JJCREP ISSN: 0910-5050. Journal written in English. CAN 103:153496 AN 1985:553496 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

5'-Deoxy-5-fluorouridine (5-DFUR)(I) [3094-09-5] was evaluated for antitumor activity against 4 murine tumors (L1210 leukemia, P388 leukemia, Lewis lung carcinoma, and B16 melanoma) and a human mammary carcinoma (MX-1) xenografted in athymic mice. I.p. administration of 5'-DFUR was ineffective against B16 melanoma implanted i.p. and showed less marked antitumor activity against P388 and L1210 leukemias implanted i.p. or i.v. as compared with that of 5-fluorouracil (5-FU) or 1-(2-tetrahydrofuryl)-5-fluorouracil (FT-207), whereas oral administration of 5'-DFUR showed a similar or superior antitumor activity to that of 5-FU or FT-207 against L1210 leukemia implanted s.c. 5'-DFUR showed a marked antitumor activity against MX-1 implanted s.c. and also showed slight antitumor activity against Lewis lung carcinoma implanted s.c. whereas 5-FU and FT-207 did not show any significant antitumor activity against these tumors. Thus 5'-DFUR may be worthy of clin. trial against solid tumors, esp. cancers of the breast.



I

Answer 34:

Bibliographic Information

Chemosensitivity of human gastrointestinal and breast cancer xenografts in nude mice. Fujita, Fumiko; Fujita, Masahide; Kimoto, Yasuhiko; Shimozuma, Kojiro; Taguchi, Tetsuo. Res. Inst. Microb. Dis., Osaka Univ., Osaka, Japan. Gan to Kagaku Ryoho (1985), 12(2), 353-61. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 102:160155 AN 1985:160155 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Exptl. chemotherapies for 15 human cancers xenografted into nude mice were performed using 14 anticancer agents including 6 drugs in clin. use. Treatment with each single agent was performed for every cancer line using the max. tolerated dose following continuous daily (antimetabolites) or intermittent (cytocidal agents) schedules. Generally, the exptl. results for each drug on the xenografts was in good accordance with the known clin. effects of each drug on the same type of cancer. On the other hand, individual cancer xenografts showed considerable differences in chemosensitivity. Some tumors were sensitive to a majority of the drugs, whereas some were resistant to many of them. Each cancer line seemed to retain individuality in its spectrum of chemosensitivity irresp. of whether it derived from the same organ or whether it was of similar histol. type. Apparently, selection of drugs is necessary for a specific type of tumor.

Answer 35:

Bibliographic Information

Experimental chemotherapy with fluoropyrimidine compounds on human gastrointestinal and breast cancers xenografted to athymic nude mice. Fujita, Masahide; Fujita, Fumiko; Nakano, Yosuke; Taguchi, Tetsuo. Res. Inst. Microb. Dis., Osaka Univ., Osaka, Japan. International Congress Series (1984), 647(Fluoropyrimidines Cancer Ther.), 121-32. CODEN: EXMDA4 ISSN: 0531-5131. Journal written in English. CAN 102:142866 AN 1985:142866 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In treatment of nude mice bearing human gastrointestinal and breast cancer xenografts with antitumor drugs (25-30 mg/kg/day), tegafur [17902-23-7] was effective in 6 out of 15 human cancer lines (40%) and uracil-tegafur mixt. (UFT) [74578-38-4] and 5'-deoxy-5-fluorouridine (5'DFUR) [3094-09-5] were both effective in 11 out of 15 lines (73%). Among the 3 drugs, 5'DFUR led the most frequently to the shrinkage of treated tumors.

Answer 36:

Bibliographic Information

Effects of 5'-deoxy-5-fluorouridine on human gastrointestinal and breast cancers xenografted to nude mice. Fujita, Fumiko; Fujita, Masahide; Taguchi, Tetsuo. Res. Inst. Microb. Dis., Osaka Univ., Osaka, Japan. Gan to Kagaku Ryoho (1984), 11(8), 1635-43. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 101:183573 AN 1984:583573 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

As a preclin. secondary screening trial, the efficacy of a new deriv. of 5-fluorouracil, 5'-deoxy-5-fluorouridine (5'-DFUR), [3094-09-5] on 15 human cancers xenografted serially to nude mice of BALB/c background was evaluated in comparison with 2 other derivs., tegafur and UFT. Oral administration of 123 mg/kg/day of 5'-DFUR, 25-30 times, produced effective inhibition in 5 out or 7 gastric cancers, 2 out of 3 colorectal cancers, all 3 of breast cancers and 1 out of 2 pancreatic cancers, totalling 11 out of 15 cancer lines (73%) examd. In some cases shrinkage of tumors was noted without any noticeable side effects. Although an increased dose of 185 mg/kg/day of 5'-DFUR resulted in more prominent inhibition on all 9 tumors tested, some animals suffered from severe loss of body wt. or diarrhea. Comparative expts. with equimolar doses of 5'-DFUR(123 mg/kg) and FT-207(100 mg/kg) showed that the inhibition rate of the former was higher than that of the latter in all 8 lines of cancers examd. Six expts. in particular (2 gastric, 1 colorectal, 2 breast and 1 pancreatic cancers), showed that 5'-DFUR statistically sustained more effective suppression. Direct comparisons of 5'-DFUR and UFT were also made in 5 expts. in which 3 cancers were more sensitive to the former drug. Promising results in clin. trials can be expected with the new drug 5'-DFUR for these kinds of cancers.

Answer 37:

Bibliographic Information

Chemosensitivity of human gastrointestinal and breast cancer xenografts in nude mice and predictability to clinical response of anticancer agents. Fujita, M.; Fujita, F.; Taguchi, T. Dep. Oncol. Surg., Osaka Univ., Osaka, Japan. Editor(s): Sordat, Bernard. Immune-Defic. Anim., Int. Workshop Immune-Defic. Anim. Exp. Res., 4th (1984), Meeting Date 1982, 311-15. Publisher: Karger, Basel, Switz CODEN: 51ONAB Conference written in English. CAN 101:103450 AN 1984:503450 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effectiveness of 13 drugs against 14 lines of human gastrointestinal and breast cancers xenografted in nude mice was studied. Despite identical origins of organ and similarities in histol. types, degrees of differentiation, and growth rate, each line of cancer

demonstrated different spectra of sensitivity to various agents. The effectiveness of various chemotherapeutic agents against human gastric cancer xenografts in nude mice was compared with the clin. effects of these drugs in clin. trials and phase II studies. The results indicated that the nude mouse-human cancer system would be useful in preclin. secondary screening.

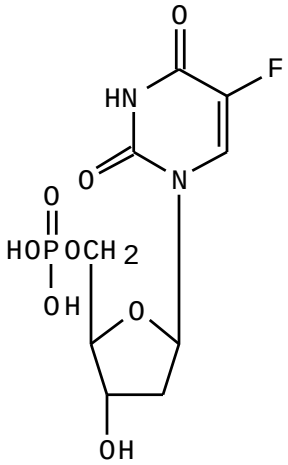
Answer 38:

Bibliographic Information

The effect of derivatives of folic acid on the fluorodeoxyuridylate-thymidylate synthetase covalent complex in human colon xenografts. Houghton, Janet A.; Schmidt, Colleen; Houghton, Peter J. Dep. Biochem. Clin. Pharmacol., St. Jude Child.'s Res. Hosp., Memphis, TN, USA. European Journal of Cancer & Clinical Oncology (1982), 18(4), 347-54. CODEN: EJCODS ISSN: 0277-5379. Journal written in English. CAN 97:156038 AN 1982:556038 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Endogenous concns. of 5,10-methylenetetrahydrofolate (I) [3432-99-3] in human colorectal adenocarcinoma xenografts were detd. Further, the ability of other folate derivs. to increase the formation of the ternary covalent complex between I, 3H-labeled 5-fluorodeoxyuridylate (FdUMP) (II) and thymidylate synthetase (EC 2.1.1.45) was studied. Concns. of I were low, ranging from 66 to 233 nM in cell water. tetrahydrofolate (FH4) [135-16-0] and dihydrofolate (FH2) [4033-27-6] increased complex formation, whereas 5-formyltetrahydrofolate [58-05-9] and 5-methyltetrahydrofolate (5-CH3FH4) [134-35-0] decreased the covalent binding of [6-3H]-FdUMP in vitro. Administration of FH4 or FH2 to tumor-bearing mice reduced subsequent formation of the covalent complex in vitro. Since 5-CH3FH4 is a major deriv. of folate in mammalian tissues, its effect on the covalent binding of [6-3H]-FdUMP was examd. further; even in the presence of homocysteine [6027-13-0] and cyanocobalamin (B12) [68-19-9], the formation of the covalent complex was not increased. The fate of [5-14CH3]-FH4 was subsequently examd. in vivo. In tumors at 1 h after injection, 72% of the radiolabel remained as [5-14CH3]-FH4, while 17% had been converted to 14C-labeled methionine or incorporated into protein. By contrast, however, the incorporation of radiolabel into the protein fraction of liver was almost 30-fold greater at this time. At 4 h, radioactivity in tumors (dpm/g) and in the fraction assocd. with [5-14CH3]-FH4 was decreased by over 60%, whereas metab. was increased by only 13%. No polyglutamate forms of [5-14CH3]-FH4 were detected in tumors at 4 h after treatment.



II

Answer 39:

Bibliographic Information

Changes of gene expression of thymidine phosphorylase, thymidylate synthase, dihydropyrimidine dehydrogenase after the administration of 5'-deoxy-5-fluorouridine, paclitaxel and its combination in human gastric cancer xenografts. Sakurai Yoichi; Yoshida Ikuo; Kamoshida Shingo; Inaba Kazuki; Isogaki Jun; Komori Yoshiyuki; Uyama Ichiro; Tsutsumi Yutaka Department of Surgery, Fujita Health University School of Medicine,

Toyoake, Aichi 470-1192, Japan. ysakurai@fujita-hu.ac.jp Anticancer research (2008), 28(3A), 1593-602. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 18630517 AN 2008455778 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Although a variety of combination chemotherapies has been tested in gastric carcinoma, the most effective chemotherapeutic regimen and the precise mechanisms underlying anticancer agent combination have not yet been sufficiently elucidated. MATERIALS AND METHODS: Experimental chemotherapy was performed using human gastric carcinoma xenografts, MKN-45 and TMK-1, to examine the anticancer effects and gene expressions of the enzymes involved in 5-fluorouracil metabolism, thymidine phosphorylase (dThdPase), thymidylate synthase (TS) and dihydropyrimidine dehydrogenase (DPD). Nude mice were treated with 5'-deoxy-5-fluorouridine (5'-dFUrd), or paclitaxel alone or in combination. The in vivo antitumor effects on gene expressions of the enzymes were examined using the quantitative real-time RT-PCR method. RESULTS: The combined use of 5'-dFUrd and paclitaxel showed additive to synergistic antitumor effects on both gastric cancer xenografts. There were significant differences of the gene expressions of dThdPase, TS, and DPD between the xenografts. The expression of dThdPase mRNA was consistently up-regulated by the administration of paclitaxel, while no constant direction of TS mRNA and DPD mRNA change was found in the xenografts. CONCLUSION: A synergistic antitumor effect of the combined administration of 5'-dFUrd and paclitaxel was found in gastric cancer xenografts and up-regulation of dThdPase mRNA may be an important underlying mechanism especially in tumors with high gene expression of this enzyme.

Answer 40:

Bibliographic Information

The Hollow Fibre Assay as a model for in vivo pharmacodynamics of fluoropyrimidines in colon cancer cells. Temmink O H; Prins H-J; van Gelderop E; Peters G J Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands British journal of cancer (2007), 96(1), 61-6. Journal code: 0370635. ISSN:0007-0920. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17179993 AN 2007016737 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The Hollow Fibre Assay (HFA) is usually applied as an early in vivo model for anti-cancer drug screening, but is potentially an excellent model for short-term in vivo pharmacodynamic studies. We used the model to study the in vivo role of thymidine phosphorylase/platelet-derived endothelial cell growth factor (TP/PD-ECGF) in the cytotoxicity and pharmacodynamics of TAS-102 in colon cancer cells. TAS-102 is a new oral drug formulation, which is composed of trifluorothymidine (TFT) and thymidine phosphorylase inhibitor (TPI), which prevents TFT degradation. We compared the activity with Xeloda (capecitabine), which is activated by TP into 5FU. Hollow fibres filled with human Colo320 or Colo320TP1 colorectal cancer cells with deficient or high TP expression, respectively, were implanted subcutaneously (s.c.) at both flanks of BALB/c mice. The mice were treated orally over 5 days with TAS-102, TFT alone, 5'DFUR+/-TPI or capecitabine at their maximum tolerated dose (MTD). The cells were retrieved from the fibres and assayed for growth (MTT assay), cell cycle distribution (flow cytometry) and apoptosis induction (FragEL method). TAS-102 induced considerable growth inhibition (50%, $P<0.01$) to both cell lines, which was completely abolished in the absence of TPI. Capecitabine and its metabolite 5'DFUR reduced proliferation of Colo320TP1 cells in the fibres significantly (down to 25-40%), but much less in Colo320 cells, whereas addition of TPI reduced the effect of 5'DFUR, although not completely. These differences in cytotoxic effects were reflected in the pharmacodynamic evaluation. TAS-102 induced a G2M-phase arrest (from 25 to 40%) and apoptosis (>8-fold), which was more pronounced in Colo320 than in Colo320TP1. Again, omission of TPI neutralised the effect of TAS-102. Similarly, 5'DFUR and capecitabine induced a significant G2M-phase arrest (up to 45%) in the Colo320TP1 cell line, but less pronounced in the parental Colo320. Addition of TPI to 5'DFUR reduced this effect to control levels.

Also induction of apoptosis was reduced in the presence of TPI. The data demonstrated that the HFA is excellently suited for studying short-term pharmacodynamic effects of fluoropyrimidines in vivo. TAS-102 is only effective in inducing cytotoxicity when systemic TPI is present, but acts against both low and high TP expressing colon cancer cells, while 5'DFUR needs cellular TP to exert significant activity.

Answer 41:

Bibliographic Information

Rational combinations of trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer. Comment in: J Natl Cancer Inst. 2004 May 19;96(10):725-7. PubMed ID: 15150294 Pegram Mark D; Konecny Gottfried E; O'Callaghan Carminda; Beryt Malgorzata; Pietras Richard; Slamon Dennis J Division of Hematology/Oncology, Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles 90095-7077, USA Journal of the National Cancer Institute (2004), 96(10), 739-49. Journal code: 7503089. E-ISSN:1460-2105. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 15150302 AN 2004251719 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Trastuzumab, a humanized anti-HER2 antibody, increases the clinical benefit of first-line chemotherapy in patients with metastatic breast cancers that overexpress HER2. We characterized interactions between trastuzumab and chemotherapeutic agents commonly used in the treatment of breast cancer. METHODS: Multiple drug effect/combination index isobologram analysis was used to study the efficacy of chemotherapeutic drug plus trastuzumab combinations tested against four HER2-overexpressing breast cancer cell lines (SK-BR-3, BT-474, MDA-MB-361, and MDA-MB-453). Combination index values were derived from parameters of the median effect plots, and statistical tests were used to determine whether the mean combination index values at multiple effect levels were statistically significantly different from a combination index value of 1.0. Values less than 1.0 indicate synergistic interactions, values greater than 1.0 indicate antagonistic interactions, and values equal to 1.0 indicate additive interactions. RESULTS: At a wide range of clinically achievable drug concentrations, synergistic interactions were observed in all four breast cancer cell lines for trastuzumab plus carboplatin (mean combination index values ranged from 0.32 [P<.001] to 0.53 [P<.001]), 4-hydroxycyclophosphamide (mean combination index values ranged from 0.38 [P<.001] to 0.73 [P =.010]), docetaxel (mean combination index values ranged from 0.30 [P<.001] to 0.62 [P<.001]), and vinorelbine (mean combination index values ranged from 0.24 [P<.001] to 0.78 [P<.034]). Additive interactions were observed in all four cell lines with trastuzumab plus doxorubicin, epirubicin, and paclitaxel. Interactions between trastuzumab and gemcitabine were synergistic at low concentrations of gemcitabine and antagonistic at high concentrations. A synergistic interaction was observed with a three-drug combination of docetaxel plus carboplatin plus trastuzumab in SK-BR-3 cells (mean combination index value = 0.09; P<.001).

CONCLUSION: Consistent synergistic interactions of trastuzumab plus carboplatin, 4-hydroxycyclophosphamide, docetaxel, or vinorelbine across a wide range of clinically relevant concentrations in HER2-overexpressing breast cancer cells indicate that these are rational combinations to test in human clinical trials.

Answer 42:

Bibliographic Information

gamma-Hydroxybutyric acid and 5-fluorouracil, metabolites of UFT, inhibit the angiogenesis induced by vascular endothelial growth factor. Basaki Y; Chikahisa L; Aoyagi K; Miyadera K; Yonekura K; Hashimoto A; Okabe S; Wierzba K; Yamada Y Cancer Research Laboratory, Taiho Pharmaceutical Co., Ltd, Hanno City, Saitama, Japan. y-basaki@taiho.co.jp Angiogenesis (2001), 4(3), 163-73. Journal code: 9814575. ISSN:0969-6970. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11911014 AN 2002178982 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

UFT, a drug composed of uracil and tegafur at the molar ratio of 4:1, is an orally active agent for the treatment of a wide variety of malignant tumours. Using a murine dorsal air sac (DAS) assay, we have previously shown that UFT and its metabolites, gamma-hydroxybutyric acid (GHB) and 5-fluorouracil (5-FU), inhibited the angiogenesis induced by murine renal cell carcinoma. Here we report that UFT was more effective than other fluorinated pyrimidines such as 5-FU and doxifluridine (5'-DFUR) in blocking the angiogenic responses elicited by five human cancer cell lines which produced high levels of vascular endothelial growth factor (VEGF), but no detectable fibroblast growth factor-2 (FGF-2) in vitro. In contrast, UFT was unable to block the angiogenic response to one human gastric cancer cell line which produced both VEGF and FGF-2 in vitro. However, the production or secretion of VEGF by these cells was unaffected by GHB and 5-FU treatment. Interestingly, GHB suppressed the chemotactic migration and tube formation of human umbilical vein endothelial cells (HUVECs) stimulated by VEGF, without inhibiting their DNA synthesis. Since GHB did not affect the FGF-2-driven activities in HUVECs, its action appears to be VEGF-selective. On the other hand, 5-FU inhibited DNA synthesis and migration of HUVECs stimulated by both VEGF and FGF-2, and tube formation driven by VEGF, suggesting that 5-FU is cytotoxic to endothelial cells. The inhibitory effects of 5-FU, and especially those GHB, were reproduced under in vivo condition using the DAS assay. The VEGF-mediated angiogenesis was significantly inhibited by UFT, 5-FU, and especially by GHB. We propose that the selective inhibitory effects of GHB on VEGF-mediated responses of endothelial cells are involved in the anti-angiogenic activity of UFT.

Answer 43:

Bibliographic Information

Enhancement of sensitivity to capecitabine in human renal carcinoma cells transfected with thymidine phosphorylase cDNA. Morita T; Matsuzaki A; Tokue A Department of Urology, Jichi Medical School, Tochigi, Japan. moritatu@jichi.ac.jp International journal of cancer. Journal international du cancer (2001), 92(3), 451-6. Journal code: 0042124. ISSN:0020-7136. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 11291085 AN 2001218011 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The purpose of the present study was to examine directly the role of thymidine phosphorylase (TP) in the sensitivity of renal cell carcinoma (RCC) to a novel fluoropyrimidine carbamate, capecitabine. TP cDNA-transfected RCC are used in these experiments to provide a basis for improved therapeutic benefit in chemoimmunotherapy. Human RCC line KU2 cells were transfected with pcDNA3.1/zeo(+) with or without human TP cDNA by the lipofectin method. We established a clone transfected with pcDNA3.1/zeo(+)/TP (KU2-TP15) and a clone transfected with pcDNA3.1/zeo(+) as a control (KU2-C1). TP expression levels (mean +/- SD) examined by enzyme-linked immunosorbent assay (ELISA) were 1.3 +/- 0.14 U/mg protein in KU2, 1.6 +/- 0.57 U/mg protein in KU2-C1 and 216 +/- 25.6 U/mg protein in KU2-TP15. Immunohistochemical staining of subcutaneous tumors established in Balb/c nu/nu mice showed that KU2-TP15 was strongly positive for TP expression, whereas KU2 and KU2-C1 were negative. Sensitivities in vitro to 5-fluorouracil (5FU), 5'-deoxy-5-fluorouridine (5'DFUR) and capecitabine in KU2-TP15 were significantly enhanced compared with those in KU2 or KU2-C1. A moderate but statistically significant bystander effect was observed in vitro. KU2-TP15 tumors showed significant increase in the in vivo sensitivities to 5'DFUR and capecitabine as compared with the vehicle alone while KU2-C1 tumors did not. The difference in tumor-free rate in mice bearing KU2-TP15 at 2 months after the cessation of treatment was statistically significant between the capecitabine treatment group and the controls, the 5FU treatment group and the 5'DFUR treatment group. The present study clearly provides direct evidence for the role of TP in mediating the sensitivity of RCC to capecitabine.

Answer 44:

Bibliographic Information

Antitumor effect of 22-oxacalcitriol on estrogen receptor-negative MDA-MB-231 tumors in athymic mice. Matsumoto H; Iino Y; Koibuchi Y; Andoh T; Horii Y; Takei H; Horiguchi J; Maemura M; Yokoe T; Morishita Y Second Department of Surgery, Gunma University School of Medicine, Maebashi, Gunma 371-8511, Japan Oncology reports

(1999), 6(2), 349-52. Journal code: 9422756. ISSN:1021-335X. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 10023003 AN 1999148162 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The purpose of this study was to evaluate the usefulness of 22-oxacalcitriol (OCT) in the treatment of estrogen receptor (ER)-negative breast cancer. The antitumor effect of this agent and its effect combined with doxifluridine (5'-DFUR) on MDA-MB-231 tumors in female athymic mice were investigated. We also examined the effect of OCT on the expression of vascular endothelial growth factor (VEGF) which had been reported to generate angiogenesis in tumors. OCT significantly suppressed the growth of tumors without inducing hypercalcemia in a dose dependent manner. The effect of OCT combined with 5'-DFUR did not exceed the effect of a single agent therapy. The expressions of VEGF analyzed by enzyme-linked immunosorbent assay were significantly decreased in the OCT-treated group. These results suggest that OCT may partially suppress tumor growth by inhibiting neovascularization and it would likely have positive application as a treatment of ER-negative breast cancer.

Answer 45:

Bibliographic Information

Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Miwa M; Ura M; Nishida M; Sawada N; Ishikawa T; Mori K; Shimma N; Umeda I; Ishitsuka H Nippon Roche Research Centre, Kanagawa, Japan European journal of cancer (Oxford, England : 1990) (1998), 34(8), 1274-81. Journal code: 9005373. ISSN:0959-8049. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9849491 AN 1999066353 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine) is a novel oral fluoropyrimidine carbamate, which is converted to 5-fluorouracil (5-FU) selectively in tumours through a cascade of three enzymes. The present study investigated tissue localisation of the three enzymes in humans, which was helpful for us to design the compound. Carboxylesterase was almost exclusively located in the liver and hepatoma, but not in other tumours and normal tissue adjacent to the tumours. Cytidine (Cyd) deaminase was located in high concentrations in the liver and various types of solid tumours. Finally, thymidine phosphorylase (dThdPase) was also more concentrated in various types of tumour tissues than in normal tissues. These unique tissue localisation patterns enabled us to design capecitabine. Oral capecitabine would pass intact through the intestinal tract, but would be converted first by carboxylesterase to 5'-deoxy-5-fluorocytidine (5'-dFCyd) in the liver, then by Cyd deaminase to 5'-deoxy-5-fluorouridine (5'-dFUrd) in the liver and tumour tissues and finally by dThdPase to 5-FU in tumours. In cultures of human cancer cell lines, the highest level of cytotoxicity was shown by 5-FU itself, followed by 5'-dFUrd. Capecitabine and 5'-dFCyd had weak cytotoxic activity only at high concentrations. The cytotoxicity of the intermediate metabolites 5'-dFCyd and 5'-dFCyd was suppressed by inhibitors of Cyd deaminase and dThdPase, respectively, indicating that these metabolites become effective only after their conversion to 5-FU. Capecitabine, which is finally converted to 5-FU by dThdPase in tumours, should be much safer and more effective than 5-FU, and this was indeed the case in the HCT116 human colon cancer and the MX-1 breast cancer xenograft models.

Answer 46:

Bibliographic Information

Positive correlation between the efficacy of capecitabine and doxifluridine and the ratio of thymidine phosphorylase to dihydropyrimidine dehydrogenase activities in tumors in human cancer xenografts.

Ishikawa T; Sekiguchi F; Fukase Y; Sawada N; Ishitsuka H Cytostatics Group, Nippon Roche Research Center, Kamakura-City, Kanagawa, Japan Cancer research (1998), 58(4), 685-90. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 9485021 AN 1998143552 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine) is a new fluoropyrimidine carbamate, which is converted to 5-fluorouracil (5-FUra) selectively in tumors through the intermediate metabolite 5'-deoxy-5-fluorouridine (5'-dFUrd, doxifluridine). 5'-dFUrd is metabolized to 5-FUra by thymidine phosphorylase (dThdPase) located in high levels in various types of solid tumors from patients, whereas 5-FUra generated is catabolized to dihydrofluorouracil by dihydropyrimidine dehydrogenase (DPD). The present study investigated whether the efficacy of capecitabine and its intermediate metabolite 5'-dFUrd correlates with levels of these enzymes in various human cancer xenograft models. Capecitabine and 5'-dFUrd were highly effective and inhibited tumor growth by more than 50% in 18 of 24 xenograft lines (75%) and 15 of 24 xenograft lines (63%), respectively, whereas 5-FUra and a mixture of tegafur and uracil were effective only in 1 of 24 (4.2%) and 5 of 24 (21%), respectively. The efficacy of capecitabine correlated with dThdPase activity. However, capecitabine was effective even in tumors with lower levels of dThdPase if DPD levels were also lower. In contrast, it was not as effective even in tumors with sufficient levels of dThdPase if DPD levels were very high. The efficacy of capecitabine consequently correlated very well with and depended on the ratio of these two enzymes in tumors. These results indicate that capecitabine might exert its efficacy through 5-FUra generated in tumor tissues but not through that generated in normal organs. On the other hand, there was no correlation between the efficacy of a mixture of tegafur and uracil and these enzyme activities in tumors. The efficacy of capecitabine would be optimized by selecting patients who have tumors with a high ratio of dThdPase to DPD activities.

Answer 47:

Bibliographic Information

Efficacy of combination chemotherapy of cyclophosphamide and 5'-deoxy-5-fluorouridine in a mammary tumor xenograft model, MX-1. Endo M; Fujimoto-Ouchi K; Matsumoto T; Tanaka Y; Ishitsuka H Nippon Roche Research Center Gan to kagaku ryoho. Cancer & chemotherapy (1997), 24(10), 1295-301. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 9279349 AN 97425299 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Efficacy of long-term combination chemotherapy of cyclophosphamide (CPA) and 5'-deoxy-5-fluorouridine (5'-DFUR), both of which have been widely used as chemotherapeutics against breast cancer patients, was examined in a mammary tumor xenograft model, MX-1. 5'-DFUR suppressed the tumor growth over a long period and prolonged the survival, although it did not reduce the initial tumor burden, CPA induced the disappearance of the tumor burden temporarily. However, CPA became inaffective despite continuation of treatment, and induced the recurrence of the tumor. The combination of these two drugs dramatically reduced the tumor burden, and suppressed the recurrence of the tumor over a long period. The tumor recurring during CPA monotherapy was resistant to CPA but susceptible to 5'-DFUR, which could be a reason for the long-lasting activity of the combination therapy. These results indicate that CPA and 5'-DFUR monotherapies have different modes of antitumor activities in the long-term therapy model, and that these drugs in combination would have better therapeutic advantage than each drug given individually.

Answer 48:

Bibliographic Information

Augmentation of chemotherapeutic efficaciousness of UFT by oral l-leucovorin--growth-inhibitory activity of

combination against human tumor xenograft. Saito H; Okabe H; Nakano K; Fujioka A; Toko T; Takeda S; Unemi N Anticancer and Antimicrobials Research Lab., Taiho Pharmaceutical Co., Ltd Gan to kagaku ryoho. Cancer & chemotherapy (1995), 22(13), 1919-25. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 7487121 AN 96083692 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Combination chemotherapy with FUra and LV has been reported as a useful treatment for patients suffering from colon carcinoma. Usually, both FUra and LV are administered by intravenous infusion, but not orally. UFT, an anti-neoplastic agent consisting of FT and uracil, is widely used for oral administration in Japan. Using human tumor xenografts of 10 cell lines, we evaluated the efficacy of UFT combined with l-LV, which is the active form of LV, by oral administration. Combined treatment of UFT with l-LV was more effective than UFT alone on the growth suppression of colon carcinoma (KM 20 C, Col-1) and mammary carcinoma (H-31, MX-1). When 1.85 mg/kg (5.55 mg/m2) of LV was given to tumor bearing mice, the antitumor activity of UFT was augmented and at a dose of 5.56 mg/kg (16.7 mg/m2) of LV, it was significantly augmented. Among various 5-FU derivatives, such as UFT, 5'-DFUR or FUra, combined treatment using UFT with l-LV was the most effective by oral administration. l-LV did not improve the anti-tumor efficacy or toxicity of 5'-DFUR. l-LV seemed to augment the anti-tumor activity of FUra, but not significantly. These results suggest that combination chemotherapy of UFT with LV is a promising approach for the clinical treatment of human colon cancer.

Answer 49:

Bibliographic Information

Remarkable antitumor activity of 5'-deoxy-5-fluorouridine in human colorectal tumor xenografts. De Cesare M; Pratesi G; De Braud F; Zunino F; Stampino C G Division of Experimental Oncology B, Istituto Nazionale per 1o Studio e la Cura dei Tumori, Milan, Italy Anticancer research (1994), 14(2A), 549-54. Journal code: 8102988. ISSN:0250-7005. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 8017859 AN 94288536 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

5'-Deoxy-5-fluorouridine (doxifluridine) is a prodrug of 5-fluorouracil (5FU) selectively activated by tumor cells. Since in clinical studies the side effects of doxifluridine differed after intravenous (i.v.) or oral administration, and oral route was the most promising in preclinical studies with murine models, in this study the drug was tested orally against a panel of human colorectal tumor xenografts with varying degrees of sensitivity to 5FU. Doxifluridine efficacy was comparable to that of 5FU when it was delivered according to a weekly schedule, but it was statistically higher when it was delivered more frequently. Impressive tumor inhibition (between 90 and 97%) was achieved in 4 out of 5 tumor lines after treatments delivered twice a week or daily 5 times a week. No difference in 5FU activity was observed between weekly and biweekly treatments, or between oral and i.v. injections. Moreover, in one tumor line in which different dosages of doxifluridine were investigated, a marked antitumor effect was obtained with a wide range of tolerated doses (4000-8000 mg/kg). Overall, these data indicated that doxifluridine is well tolerated when given orally and frequently. Using an adequate schedule, the prodrug has a better therapeutic efficacy against a variety of human colon cancer models than 5FU.

Answer 50:

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Fluoropyrimidine metabolism in human head and neck cancer xenografts and murine colon tumors. Laurensse E J; Braakhuis B J; Pinedo H M; Peters G J Department of Oncology, Free University Hospital, Amsterdam,

the Netherlands Advances in experimental medicine and biology (1989), 253B 327-34. Journal code: 0121103. ISSN:0065-2598. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2532861 AN 90119199 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 51:

Bibliographic Information

The antiproliferative effects of fluoropyrimidine derivatives against human tumor xenografts in a subrenal capsule assay. Nishiyama M; Takagami S; Kirihara Y; Saeki T; Hirabayashi N; Nosoh Y; Niimoto M; Hattori T Department of Surgery, Hiroshima University, Japan The Japanese journal of surgery (1988), 18(6), 725-8. Journal code: 1302176. ISSN:0047-1909. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2977626 AN 89236816 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The antiproliferative effects of the fluoropyrimidine derivatives, 5-fluorouracil (5-FU), 1-(2-tetrahydrofuryl)-5-fluorouracil (Tegafur), UFT, 1-hexylcarbamoyl-5-fluorouracil (HCFU), and 5'-deoxy-5-fluorouracil (5'DFUR), were investigated in a 4 day subrenal capsule assay. The antiproliferative effects against two human tumor xenografts established in athymic mice were examined after treatment with three different doses of each anticancer agent, and the adequate dose of each anticancer agent in this experimental system was estimated as: 473 mg/kg for Tegafur, 433 mg/kg for UFT, 50 mg/kg for HCFU and 185 mg/kg for 5'DFUR, respectively. A comparative study of the antiproliferative effects of fluoropyrimidine derivatives was carried out against 7 xenografts. According to our criteria of positive tumor response, the effective rates were: 1 of 7 (14.3 per cent) by 5-FU, 2 of 7 (28.6 per cent) by Tegafur, 2 of 7 (28.6 per cent) by UFT, 1 of 6 (16.7 per cent) by HCFU, and 1 of 4 (25.0 per cent) by 5'DFUR, respectively. Although no statistical differences were demonstrated between the agents, the utility of a chemosensitivity test before clinical use was suggested.

Answer 52:

Bibliographic Information

Enhanced therapeutic efficacy of 5'deoxy-5-fluorouridine in 5-fluorouracil resistant head and neck tumours in relation to 5-fluorouracil metabolising enzymes. Peters G J; Braakhuis B J; de Bruijn E A; Laurensse E J; van Walsum M; Pinedo H M Department of Oncology, Free University Hospital, Amsterdam, The Netherlands British journal of cancer (1989), 59(3), 327-34. Journal code: 0370635. ISSN:0007-0920. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2522792 AN 89194072 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Four human head and neck xenograft (HNX) tumour lines grown in nude mice and two murine colon carcinomas (Colon 26 and 38) were tested for their sensitivity to 5-fluorouracil (5-FU) and its prodrug 5'deoxy-5-fluorouridine (Doxifluridine, 5'd-FUR). 5-FU sensitivity at the maximum tolerated dose (MTD) showed the following pattern; HNX-DU less than HNX-KE = HNX-E = HNX-G less than Colon 26 much less than Colon 38. The sensitivity pattern to 5'd-FUR was: HNX-DU less than HNX-G less than HNX-E less than HNX-KE less than Colon 38 less than Colon 26. For HNX-KE, HNX-E and Colon 26 an increase in therapeutic efficacy was observed with 5'd-FUR as compared to 5-FU; Colon 38 was as sensitive to 5'd-FUR as to 5-FU. Plasma pharmacokinetics of 5'd-FUR and 5-FU were comparable in normal and nude mice. Metabolism of 5-FU and 5'd-FUR was studied in the tumours. Conversion of 5'd-FUR to 5-FU was highest in Colon 26 and 15-20 times lower in HNX-DU, HNX-KE and Colon 38. The Km for 5'd-FUR in all tumours was 1-2 mM. Further anabolism of 5-FU to fluorouridine (FUR) was 5-10 times higher than that of 5-FU to FUR in HNX tumours and 3 times in the colon tumours. 5-FU conversion to FUMP via FUR had the following pattern: Colon 26 much greater than HNX-DU greater than HNX-G greater than HNX-E greater than HNX-KE much greater than Colon 38; of 5-FU to FdUMP

via FUdR: Colon 26 greater than HNX-DU = HNX-KE greater than HNX-E greater than HNX-G = Colon 38; and that of 5-FU to FUMP catalysed by orotate phosphoribosyl transferase (OPRT); Colon 26 greater than or equal to Colon 38 greater than HNX-KE greater than HNX-E = HNX-DU = HNX-G. Only those tumours with a relatively high activity of OPRT were sensitive to 5'd-FUR. Colon 26, which has a very high rate of pyrimidine nucleoside phosphorylase, showed a relatively high increase in the therapeutic efficacy. It is concluded that a low rate of pyrimidine nucleoside phosphorylase is enough to convert 5'd-FUR to 5-FU;
further anabolism of 5-FU catalysed by OPRT may be limiting and explain the differential sensitivity.

Answer 53:

Bibliographic Information

Combined therapy of polyamine antimetabolites and antitumor drugs for human gastric cancer xenotransplanted into nude mice. Fujimoto S; Igarashi K; Shrestha R D; Miyazaki M; Endoh F; Ohta M; Togawa Y; Okui K The Japanese journal of surgery (1986), 16(2), 133-9. Journal code: 1302176. ISSN:0047-1909. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2941608 AN 86255011 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Antitumor therapies using polyamine antimetabolites combined with 1-(4-amino-2-methyl-5-pyrimidyl)methyl-3(2-chloroethyl)-3-nitrosourea (ACNU) or fluorinated pyrimidines for human gastric cancer xenotransplanted into nude mice were studied to determine inhibiting post-therapeutic regrowth of the tumor after cessation of antitumor treatments with polyamine antimetabolites alone. ACNU 20 mg/kg, fluorinated pyrimidine, 5-FU 52.8 mg/kg and 5'-deoxy-5-fluorouridine (5'-DFUR) 100 mg/kg as well as polyamine antimetabolites, alpha-difluoromethylornithine (DFMO) 1000 mg/kg and methylglyoxal-bis-guanylhydrazone (MGBG) 50 mg/kg were given intraperitoneally for 5 successive days. When DFMO and MGBG were combined with ACNU, the post-therapeutic regrowth was definitely inhibited, while combined treatments with 5-FU or 5'-DFUR did not inhibit the regrowth. Post-therapeutic DNA biosynthesis was suppressed in mice given DFMO, MGBG plus ACNU. On the contrary, in mice treated with DFMO, MGBG plus 5-FU or 5'-DFUR, suppression of DNA biosynthesis was not observed. Tumor tissue spermine levels in the DFMO, MGBG plus 5-FU or 5'-DFUR group remained unchanged, compared to those in the DFMO + MGBG group. In mice given DFMO, MGBG plus ACNU, however, spermine levels were markedly depressed; and the ACNU alone depressed also the tissue spermine levels. These different results between nitrosourea and fluorinated pyrimidines may relate to mechanisms of action of these antitumor drugs.

Answer 54:

Bibliographic Information

Anticancer treatment with a combination of antimetabolites of polyamine and pyrimidine. Fujimoto S; Shrestha R D; Igarashi K; Miyazaki M; Endoh F; Shimura T; Sugasawa H; Takahashi O; Kawata S; Ohta M; + Gan to kagaku ryoho. Cancer & chemotherapy (1985), 12(10), 2024-9. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 2932057 AN 86024325 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A combined efficacy of the polyamine antimetabolites, alpha-difluoromethylornithine (DFMO) and methylglyoxal-bis-guanylhydrazone (MGBG) with two fluorinated pyrimidines was studied. DFMO, MGBG, 5-FU and 5'-deoxy-5-fluorouridine (5'-DFUR) were administered intraperitoneally to BALB/c nu/nu mice bearing xenotransplanted human gastric cancer for 5 consecutive days. Similar antitumor efficacies were observed in 3 groups treated with DFMO plus MGBG, DFMO, MGBG plus 5-FU as well as DFMO, MGBG plus 5'-DFUR. The two groups on 5-FU or 5'-DFUR alone

did not differ in antitumor effects from the control, although reasonable levels of 5-FU were involved in tumor tissues. Hepatic and splenic 5-FU levels after 5-FU administration were significantly higher than those after 5'-DFUR, and marked decrease in mouse body weight was caused by 5-FU alone as well as 5-FU plus polyamine antimetabolites for 5 consecutive days. DNA biosynthesis and spermine levels in the tumor tissues on day 2 after cessation of the treatments dropped in 3 groups with DFMO plus MGBG, DFMO, MGBG plus 5'-DFUR as well as DFMO, MGBG plus 5-FU, while on day 6 there was little difference between the control and treated groups. These data suggest that combination with 5-FU or 5'-DFUR does not enhance the antitumor activity of polyamine antimetabolites by this experimental regimen.